INTERNATIONAL SEARCH REPORT

Inte ...onal Application No
PCT/EP 97/06652

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08F271/00 C08F8/12 B01F17/00 C09B67/00 C11D3/37
D21H17/34 C09K17/20 C05G3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08F B01F C09B C11D D21H C09K C05G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 25759 A (BASF AG ;HARTMANN HEINRICH (DE); DENZINGER WALTER (DE); NILZ CLAUD) 28 September 1995 see claim 1 ---	1,2,5
Y	US 3 249 571 A (BARTMANN ET AL.) 3 May 1966 see claims 1,2 ---	1,2,5
A	GB 1 551 513 A (TOA PAINT CO LTD) 30 August 1979 see claim 1 ---	1
A	WO 94 08092 A (BASF AG ;NILZ CLAUDIA (DE); SENDHOFF NORBERT (DE); BREITSCHAFT WAL) 14 April 1994 see claim 1 -----	1,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1998	29/04/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Meulemans, R

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/EP 97/06652

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9525759 A	28-09-95	DE 4409903 A	28-09-95
		EP 0751968 A	08-01-97
		FI 963778 A	22-11-96
		JP 9510488 T	21-10-97
US 3249571 A	03-05-66	NONE	
GB 1551513 A	30-08-79	JP 1261136 C	25-04-85
		JP 52112633 A	21-09-77
		JP 59035938 B	31-08-84
		DE 2711458 A	22-09-77
		NL 7702975 A	20-09-77
WO 9408092 A	14-04-94	DE 4233040 A	07-04-94
		AT 135431 T	15-03-96
		CA 2143747 A	14-04-94
		DE 59301914 D	18-04-96
		EP 0663031 A	19-07-95
		ES 2084513 T	01-05-96
		FI 951516 A	30-03-95
		JP 8501835 T	27-02-96
		US 5554261 A	10-09-96

INTERNATIONALER RECHERCHENBERICHT

Intern. nales Aktenzeichen
PCT/EP 97/06652

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 C08F271/00 C08F8/12 B01F17/00 C09B67/00 C11D3/37
D21H17/34 C09K17/20 C05G3/00

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 C08F B01F C09B C11D D21H C09K C05G

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	WO 95 25759 A (BASF AG ;HARTMANN HEINRICH (DE); DENZINGER WALTER (DE); NILZ CLAUD) 28.September 1995 siehe Anspruch 1 ---	1,2,5
Y	US 3 249 571 A (BARTMANN ET AL.) 3.Mai 1966 siehe Ansprüche 1,2 ---	1,2,5
A	GB 1 551 513 A (TOA PAINT CO LTD) 30.August 1979 siehe Anspruch 1 ---	1
A	WO 94 08092 A (BASF AG ;NILZ CLAUDIA (DE); SENDHOFF NORBERT (DE); BREITSCHAFT WAL) 14.April 1994 siehe Anspruch 1 -----	1,6

☐ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

☒ Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
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1

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
20.April 1998	29/04/1998
Name und Postanschrift der Internationalen Recherchenbehörde	**Bevollmächtigter Bediensteter**
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Meulemans, R

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veroffentlichungen, die zur selben Patentfamilie gehören

Interr. .ales Aktenzeichen
PCT/EP 97/06652

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
WO 9525759 A	28-09-95	DE 4409903 A	28-09-95
		EP 0751968 A	08-01-97
		FI 963778 A	22-11-96
		JP 9510488 T	21-10-97
US 3249571 A	03-05-66	KEINE	
GB 1551513 A	30-08-79	JP 1261136 C	25-04-85
		JP 52112633 A	21-09-77
		JP 59035938 B	31-08-84
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WO 9408092 A	14-04-94	DE 4233040 A	07-04-94
		AT 135431 T	15-03-96
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		EP 0663031 A	19-07-95
		ES 2084513 T	01-05-96
		FI 951516 A	30-03-95
		JP 8501835 T	27-02-96
		US 5554261 A	10-09-96

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/00167 A2

(51) International Patent Classification⁷: A61K

(21) International Application Number: PCT/US01/19750

(22) International Filing Date: 19 June 2001 (19.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

09/602,688	23 June 2000 (23.06.2000)	US
09/715,767	17 November 2000 (17.11.2000)	US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US	09/602,688 (CON)
Filed on	23 June 2000 (23.06.2000)
US	09/715,767 (CON)
Filed on	17 November 2000 (17.11.2000)

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/00167 A2

(54) Title: MODIFIED FORMS OF PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR

(57) Abstract: In accordance with the present invention, there are provided modified forms of nonsteroidal anti-inflammatory drugs (NSAIDs). Modified NSAIDs according to the invention provide a new class of anti-inflammatory agent which provides the therapeutic benefits of NSAIDs while causing a much lower incidence of side-effects then typically observed with such agents.

MODIFIED FORMS OF PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR

FIELD OF THE INVENTION

The present invention relates to novel forms of pharmacologically active agents, and methods for the preparation and use thereof. In a particular aspect of the invention, methods are provided for treating pathological conditions with a modified form of one or more pharmacologically active agents, thereby reducing the occurrence of side-effects caused thereby.

BACKGROUND OF THE INVENTION

Despite the advent of modern pharmaceutical technology, many drugs still possess untoward toxicities which often limit the therapeutic potential thereof. For example, although nonsteroid antiinflammatory drugs (NSAIDs) are a class of compounds which are widely used for the treatment of inflammation, pain and fever, NSAIDs (e.g., naproxen, aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side effect that remains the major limitation to the use of NSAIDs (see, for example, J. L. Wallace, in Gastroenterol. 112:10001016 (1997); A. H. Soll et al., in Ann Intern Med. 114:307319 (1991); and J. Bjarnason et al., in Gastroenterol. 104:18321847 (1993)).

There are two major ulcerogenic effects of NSAIDs: (1) irritant effects on the epithelium of the gastrointestinal tract and (2) suppression of gastrointestinal prostaglandin synthesis. In recent years, numerous strategies have been attempted to design and develop new NSAIDs that reduce the damage to the gastrointestinal tract. These efforts, however, have largely been unsuccessful. For example, enteric coating or slow release formulations designed to reduce the topical irritant properties of NSAIDs have been shown to be ineffective in terms of reducing the incidence of

clinically significant side effects, including perforation and bleeding (see, for example, D. Y. Graham et al., in Clin. Pharmacol. Ther. 38:6570 (1985); and J. L. Carson, et al., in Arch. Intern. Med., 147:10541059 (1987)).

It is well recognized that aspirin and other NSAIDs exert their pharmacological effects through the non-selective inhibition of cyclooxygenase (COX) enzymes, thereby blocking prostaglandin synthesis (see, for example, J. R. Van in Nature, 231:232235 (1971)). There are two types of COX enzymes, namely COX1 and COX2. COX1 is expressed constitutively in many tissues, including the stomach, kidney, and platelets, whereas COX2 is expressed only at the site of inflammation (see, for example, S. Kargan et al. in Gastroenterol., 111:445454 (1996)). The prostagladins derived from COX1 are responsible for many of the physiological effects, including maintenance of gastric mucosal integrity.

Many attempts have been made to develop NSAIDs that only inhibit COX2, without impacting the activity of COX1 (see, for example, J.A. Mitchell et al., in Proc. Natl. Acad. Sci. USA 90:1169311697 (1993); and E.A. Meade et al., in J. Biol. Chem., 268:66106614 (1993)). There are several NSAIDs presently on the market (e.g., rofecoxib and celecoxib) that show marked selectivity for COX2 (see, for example, E. A. Meade, supra.; K. Glaser et al., in Eur. J. Pharmacol. 281:107111 (1995) and Kaplan-Machlis, B., and Klostermeyer, BS in Ann Pharmacother. 33:979-88, (1999)). These drugs appear to have reduced gastrointestinal toxicity relative to other NSAIDs on the market.

On the basis of encouraging clinical as well as experimental data, the development of highly selective COX2 inhibitors appears to be a sound strategy to develop a new generation of antiinflammatory drugs. However, the physiological functions of COX1 and COX2 are not always well defined. Thus, there is a possibility that prostagladins produced as a result of COX1 expression may also contribute to inflammation, pain and fever. On the other hand, prostagladins

produced by COX2 have been shown to play important physiological functions, including the initiation and maintenance of labor and in the regulation of bone resorption (see, for example, D. M. Slater et al., in Am. J. Obstet. Gynecol., 172:7782 (1995); and Y. Onoe et al., in J. Immunol. 156:758764 (1996)), thus inhibition of this pathway may not always be beneficial. Considering these points, highly selective COX2 inhibitors may produce additional side effects above and beyond those observed with standard NSAIDs, therefore such inhibitors may not be highly desirable.

Accordingly, there is still a need in the art for modified forms of NSAIDs which cause a reduced incidence of side-effects, relative to the incidence of side-effects caused by such pharmacologically active agents in unmodified form.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a new class of modified NSAIDs which cause a much lower incidence of side-effects than are typically observed with unmodified NSAIDs due to the protective effects imparted by modifying the NSAIDs as described herein.

There are a number of advantages provided by modified NSAIDs according to the invention including one or more of the following:

(i) reduced irritant effects (e.g., contact irritation) of NSAIDs,

(ii) enhanced tissue delivery of the drug as a result of a decrease in net charges on the molecule, particularly for acidic NSAIDs such as naproxen, aspirin, diclofenac and ibuprofen, thereby reducing the quantity of material which must be delivered to achieve an effective dosage, and

(iii) reduction in the maximum concentration (C_{max}) achieved upon administration to a subject relative to the unmodified NSAID, while maintaining a therapeutically effective concentration of the NSAID in plasma of the subject.

In accordance with the present invention, cleavage of the modified NSAIDs described herein from the modified group appended thereto releases the pharmaceutically active agent.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the total length of intestinal ulcers measured after three daily doses of NSAID in unfasted male Sprague-Dawley rats (150-200 g) treated with vehicle, naproxen, or equimolar invention composition (compound 19). * $P < 0.05$ by unpaired t-test.

Figure 2 illustrates the total length of intestinal ulcers measured after 14 daily doses of NSAID in unfasted male Sprague-Dawley rats (150-200 g) treated with vehicle (bar 7), three doses of naproxen (bar 1: 50 mg/kg, bar 2: 45 mg/kg, bar 3: 40 mg/kg), or three equimolar doses of invention composition (compound 19) (bars 4-6). * $P < 0.05$ by unpaired t-test vs. corresponding dose of naproxen.

Figure 3 illustrates the inhibition of paw volume increases in the uninjected feet of Lewis male rats in which arthritis was induced by intradermal injection of adjuvant into the footpad. Rats were injected on day 0 and treated once daily from days 8 to 15 with vehicle, naproxen (10 mg/kg), or invention composition (compound 19) at equivalent dose. Paw volumes were measured with a Plethysmometer on days 5 and 15. Closed circles = naproxen; squares = invention composition.

Figure 4 compares naproxen plasma concentration-time profiles ($n = 4$, mean $\pm$ s.d.) after oral administration of naproxen (darkened circles) at 2 mg/kg and modified naproxen (open triangles) at an equivalent dose of 2 mg/kg with respect to naproxen in rats. At predetermined times, blood samples were collected and centrifuged to obtain the plasma samples. The plasma naproxen levels were measured by HPLC with a UV detection system.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds comprising a modified NSAID, wherein the NSAID is covalently attached either directly or through a linker molecule to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety. Exemplary invention compounds have the structure:

X-L-Z

wherein:

X = a non-steroidal anti-inflammatory drug (NSAID),

L = an optional linker/spacer, and

Z = a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

NSAIDs contemplated for modification in accordance with the present invention include acetaminophen (Tylenol, Datril, etc.), aspirin, ibuprofen (Motrin, Advil, Rufen, others), choline magnesium salicylate (Triasate), choline salicylate (Anthropan), diclofenac (voltaren, cataflam), diflunisal (dolobid), etodolac (lodine), fenoprofen calcium (nalfon), flurbiprofen (ansaid), indomethacin (indocin, indometh, others), ketoprofen (orudis, oruvail), carprofen, indoprofen, ketorolac tromethamine (toradol), magnesium salicylate (Doan's, magan, mobidin, others), meclofenamate sodium (meclomen), mefenamic acid (relafan), oxaprozin (daypro), piroxicam (feldene), sodium salicylate, sulindac (clinoril), tolmetin (tolectin), meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, flosulide, and the like. Presently preferred NSAIDs employed in the practice of the invention include naproxen, aspirin, ibuprofen, flurbiprofen, indomethacin, ketoprofen, carprofen, and the like. When the NSAID is aspirin, the

sulfur-containing functional groups $-CH_2S(O)_2CH_3$, $-CH_2S(O)CH_3$, and $-SCH_3$ are not presently preferred.

Invention compounds can be readily prepared in a variety of ways either by direct reaction of NSAIDs with the sulfur-containing functional group or indirectly through a suitable linker molecule.

The components of invention compositions are directly or indirectly covalently attached employing a variety of linkages (including an optional linker), e.g., ester linkages, disulfide linkages, amide linkages, immine linkages, enamine linkages, ether linkages, thioether linkages, imide linkages, sulfate ester linkages, sulfonate ester linkages, sulfone linkages, sulfonamide linkages, phosphate ester linkages, carbonate linkages, O-glycosidic linkages, S-glycosidic linkages, and the like. Such linkages can be accomplished using standard synthetic techniques as are well known by those of skill in the art, either by direct reaction of the starting materials, or by incorporating a suitable functional group on the starting material, followed by coupling of the reactants.

When the pharmacologically active agents contemplated for use herein contain suitable functionality thereon, e.g., hydroxy, amino, carboxy, and the like, invention modified NSAIDs can be prepared by direct linkage between the two agents. Alternatively, the NSAIDs can be functionalized so as to facilitate linkage between the two agents. When present, linker/spacer L has the following structure:

-W-R-

wherein:

R is optional, and when present is alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene or substituted aralkylene, and

W is ester, reverse ester, thioester, reverse thioester, amide, reverse amide, phosphate, phosphonate, imine, enamine, or the like.

Functional groups contemplated by the present invention are sulfur-based. Examples of suitable sulfur-containing functional groups include sulfonate, reverse sulfonate, sulfonamide, reverse sulfonamide, sulfone, sulfinate, reverse sulfinate, and the like. In a particular aspect of the invention, the sulfur-based moiety is sulfonate or reverse sulfonate. In a particularly preferred aspect of the invention, the sulfonate is an optionally substituted aromatic sulfonate such as tosylate or brosylate.

Other preferred sulfur-based functional groups contemplated by the present invention include sulfones. Preferably, the sulfone is an optionally substituted alkyl or aromatic sulfone.

In one aspect of the invention, Z may have the following structure:

-Y-S(O)n-Y'-Q

wherein:

each of Y and Y' are optionally present, and when present are independantly -O- or -NR'-, wherein R' is H or an optionally substituted hydrocarbyl moiety;

n is 1 or 2, and

Q is H or an optionally substituted hydrocarbyl moiety.

As employed herein, "hydrocarbyl" embraces alkyl, substituted alkyl, oxyalkyl, substituted oxyalkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, monocyclic heterocylic, substituted monocyclic heterocyclic, monocyclic aromatic, monosubstituted monocyclic aromatic, or the like.

As employed herein, "alkyl" refers to hydrocarbyl radicals having 1 up to 20 carbon atoms, preferably 2-10 carbon atoms; and "substituted alkyl" comprises alkyl

groups further bearing one or more substituents selected from hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, halogen, trifluoromethyl, cyano, nitro, nitrone, amino, amido, C(O)H, acyl, oxyacyl, carboxyl, carbamate, sulfonyl, sulfonamide, sulfuryl, and the like.

As employed herein, "oxyalkyl" refers to the moiety -O-alkyl-, wherein alkyl is as defined above, and "substituted oxyalkyl" refers to oxyalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "cycloalkyl" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "heterocyclic" refers to cyclic (i.e., ring-containing) groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic groups further bearing one or more substituents as set forth above.

As employed herein, "alkenyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "alkynyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynyl" refers to alkynylene groups further bearing one or more substituents as set forth above.

As employed herein, "monocyclic aromatic" refers to aromatic groups having in the range of 5 up to 7 carbon atoms and "monosubstituted monocyclic aromatic" refers to aromatic groups further bearing one of the substituents set forth above.

As employed herein, "alkylene" refers to divalent hydrocarbyl radicals having 1 up to 20 carbon atoms, preferably 2-10 carbon atoms; and "substituted alkylene" comprises alkylene groups further bearing one or more substituents as set forth above.

As employed herein, "cycloalkylene" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkylene" refers to cycloalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "oxyalkylene" refers to the moiety -O-alkylene-, wherein alkylene is as defined above, and "substituted oxyalkylene" refers to oxyalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkenylene" refers to divalent, straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenylene" refers to alkenylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkynylene" refers to divalent straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynylene" refers to alkynylene groups further bearing one or more substituents as set forth above.

As employed herein, "arylene" refers to divalent aromatic groups having in the range of 6 up to 14 carbon atoms and "substituted arylene" refers to arylene groups further bearing one or more substituents as set forth above.

As employed herein, "alkylarylene" refers to alkyl-substituted arylene groups and "substituted alkylarylene" refers to alkylarylene groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkylene" refers to aryl-substituted alkylene groups and "substituted arylalkylene" refers to arylalkylene groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkenylene" refers to aryl-substituted alkenylene groups and "substituted arylalkenylene" refers to arylalkenylene groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkynylene" refers to aryl-substituted alkynylene groups and "substituted arylalkynylene" refers to arylalkynylene groups further bearing one or more substituents as set forth above.

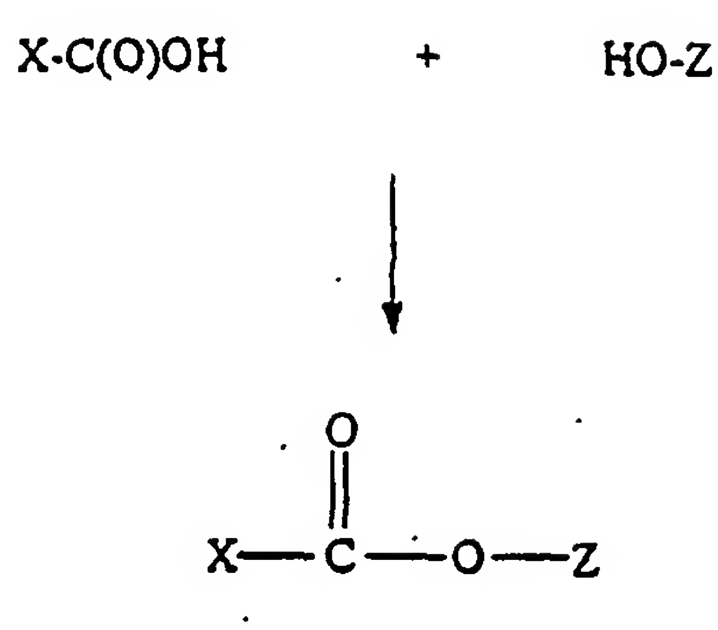
Diseases and conditions contemplated for treatment in accordance with the present invention include inflammatory and infectious diseases, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease), diabetes, arthritis (e.g., rheumatoid athritis and osteoarthritis), asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation (e.g., liver inflammation, renal inflammation, and the like), burn, infection (including bacterial,

viral, fungal and parasitic infections), hemodialysis, chronic fatigue syndrome, stroke, cancers (e.g., breast, melanoma, carcinoma, and the like), cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS, AIDS dementia, chronic neurodegenerative disease, pain (e.g., chronic pain and post-surgical pain), priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, headache, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graftversushost disease, head injury, CNS trauma, hepatitis, renal failure, liver disease (e.g., chronic hepatitis C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, postangioplasty, restenosis, angina, coronary artery disease, and the like.

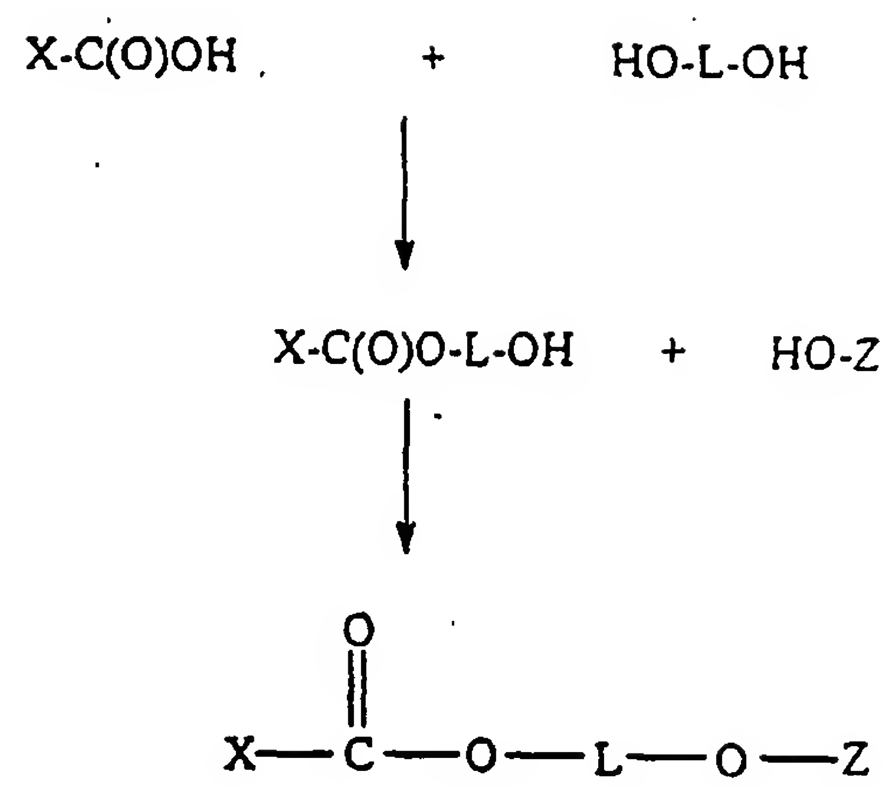
In accordance with another embodiment of the present invention, there are provided methods for the preparation of modified NSAIDs, said method comprising covalently attaching a NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety. The resulting compound provides a latent form of the pharmacologically active agent, releasing the biological activity thereof only when the compound is cleaved (e.g., by an esterase, amidase or other suitable enzyme).

As readily recognized by those of skill in the art, invention compounds can be prepared in a variety of ways. See, for example, Schemes 1A and 1B, wherein NSAID, X, bearing a carboxylic moiety can be reacted either directly with the sulfur-containing functional group (Scheme 1A) or indirectly through a linker molecule (Scheme 1B).

Scheme 1A



Scheme 1B



Employing these general reaction schemes, invention modified NSAIDs can be prepared from a wide variety of pharmacologically active agents. See, for example, Examples 1-59 provided herein.

In accordance with yet another embodiment of the present invention, there are provided methods for reducing the side effects induced by administration of NSAIDs to a subject, said method comprising reducing the C_{max} relative to unmodified NSAIDs while maintaining a therapeutically effective concentration in plasma upon administration to a subject in need thereof. The reduction in C_{max} is achieved, for example, by covalently attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID prior to administration to said subject, as depicted in Schemes 1A and 1B.

In a particular embodiment of the invention, the C_{max} is reduced relative to the unmodified NSAID by about 10% to 90%. In a presently preferred embodiment, the C_{max} is reduced relative to the unmodified NSAID by about 20% to 80%. In a most

preferred embodiment, the C_{max} is reduced relative to the unmodified NSAID by about 40% to 70%.

In accordance with still another embodiment of the present invention, there are provided methods for enhancing the effectiveness of NSAIDs, said method comprising reducing the C_{max} relative to unmodified NSAIDs while maintaining a therapeutically effective concentration in plasma upon administration to a subject in need thereof. The enhanced effectiveness of said NSAIDs is achieved, for example, by covalently attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID.

In accordance with a still further embodiment of the present invention, there are provided improved methods for the administration of NSAIDs to a subject for the treatment of a pathological condition, the improvement comprising reducing the C_{max} relative to unmodified NSAIDs while maintaining a therapeutically effective concentration in plasma upon administration to a subject in need thereof. The improvement is accomplished, for example, by covalently attaching said NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety prior to administration thereof to said subject.

Those of skill in the art recognize that the modified NSAIDs described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously, parenterally, rectally, by inhalation, and the like.

Depending on the mode of delivery employed, the modified NSAIDs contemplated for use herein can be delivered in a variety of pharmaceutically acceptable forms. For example, the invention modified NSAIDs can be delivered in the form of a solid, solution, emulsion, dispersion, micelle, liposome, and the like.

Thus, in accordance with still another embodiment of the present invention, there are provided physiologically active composition(s) comprising invention modified NSAIDs in a suitable vehicle rendering said compounds amenable to oral delivery, transdermal delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a micelle, a liposome, and the like, wherein the resulting composition contains one or more of the modified NSAIDs of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. Invention modified NSAIDs may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Invention modified NSAIDs are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing invention modified NSAIDs may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in

order to provide pharmaceutically elegant and palatable preparations. Tablets containing inventon modified NSAIDs in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the invention modified NSAIDs are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the invention modified NSAIDs are mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable

oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Invention modified NSAIDs contemplated for use in the practice of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the invention modified NSAIDs with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

In general, the dosage of invention modified NSAIDs employed as described herein falls in the range of about 0.01 mmoles/kg body weight of the subject/hour up to about 0.5 mmoles/kg/hr. Typical daily doses, in general, lie within the range of from about 10 μg up to about 100 mg per kg body weight, and, preferably within the range of from 50 μg to 10 mg per kg body weight and can be administered up to four times daily. The daily IV dose lies within the range of from about 1 μg to about 100 mg per kg body weight, and, preferably, within the range of from 10 μg to 10 mg per kg body weight.

In accordance with yet another embodiment of the present invention, there are provided improved methods for the treatment of a subject suffering from a pathological condition by administration thereto of a NSAID , the improvement comprising reducing the C_{max} relative to unmodified NSAIDs while maintaining a

therapeutically effective concentration in plasma upon administration to a subject in need thereof. The improvement is achieved, for example, by covalently attaching said NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety prior to administration thereof to said subject.

Thus, invention method for the treatment of a subject afflicted with a pathological condition comprises administering to a subject an effective amount of a modified pharmacologically active agent,

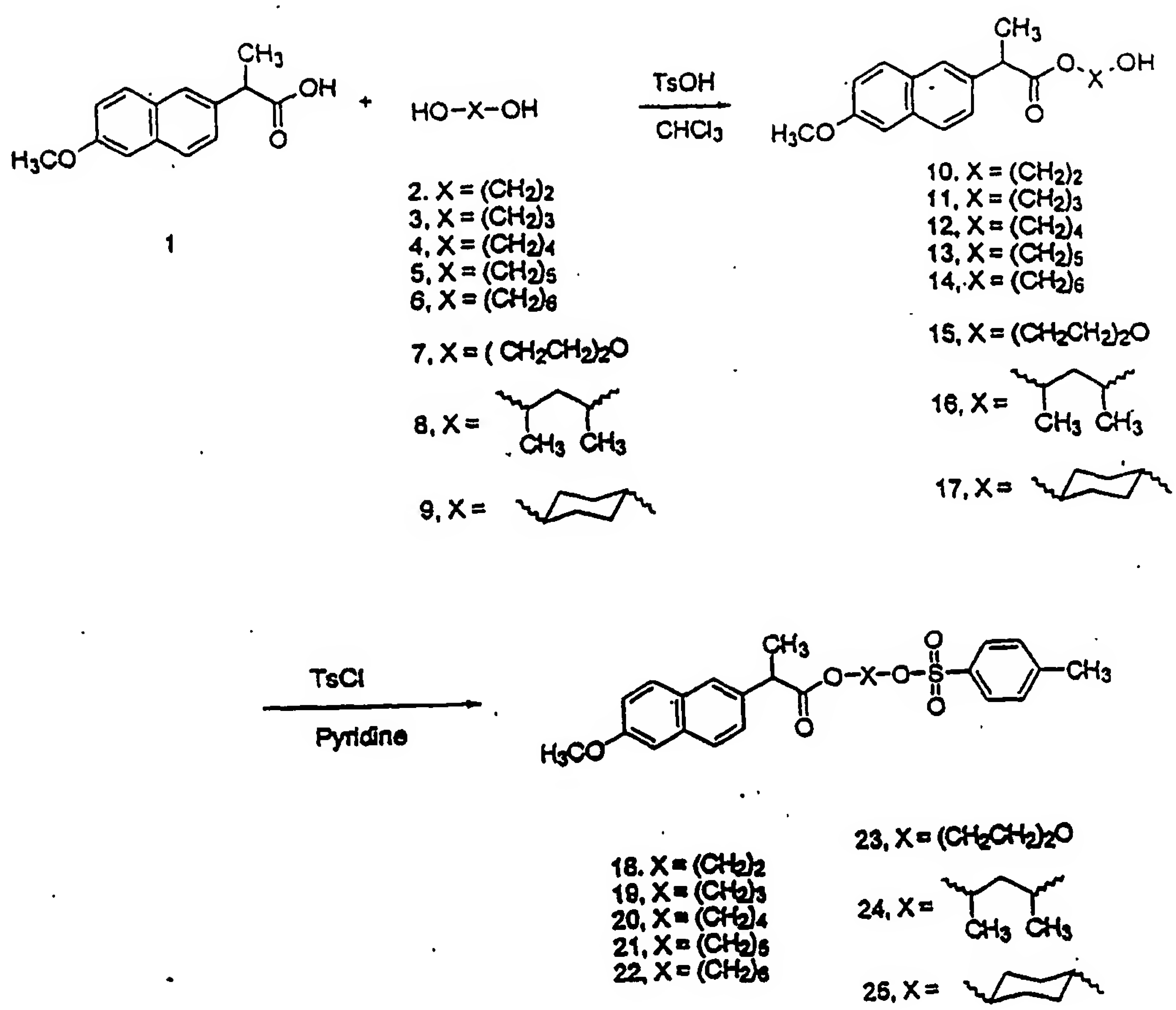
wherein said pharmacologically active agent is a NSAID, and is effective for treatment of said condition, and

wherein said pharmacologically active agent has been modified to reduce the C_{max} relative to unmodified NSAIDs while maintaining a therapeutically effective concentration in plasma upon administration to a subject in need thereof. The modification is accomplished, for example, by the covalent attachment to the NSAID of a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

The invention will now be described in greater detail by reference to the following non-limiting examples.

The syntheses described in Examples 1-8 are outlined in Scheme 2.

Scheme 2



Example 1

Compound 10 (Scheme 2). A mixture of Naproxen (1) (23 g, 0.1 mol), ethylene glycol (2) (27.9 ml, 0.5 mol) and toluenesulfonic acid (TsOH) (1.27g, 6.7 mmol) in $CHCl_3$ was heated to reflux for 4 h. The reaction solution was washed with water, 10% Na_2CO_3 solution and water. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by crystallization from CH_2Cl_2 and hexanes to give 25.7g (94%) of the compound 10 as a white crystal ; ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 3H), 1.62 (br, 1H, ex D_2O), 3.74 (t, 2H), 3.90 (q, 1H), 3.91 (s, 3H), 4.21 (t, 2H), 7.11 (m, 2H), 7.39 (d, 1H), 7.69 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 18.7, 45.6, 55.5, 61.4, 66.6, 105.8, 119.3, 126.1, 126.2, 127.5, 129.1, 129.5, 133.9, 135.7, 157.9, 175.2; MS (ESI) m/z 273 (M-1).

Compound 18 (Scheme 2). To a solution of compound 10 (24.5g, 89 mmol) in 100 ml of pyridine was added tosyl chloride (TsCl) (34.1g, 179 mmol). The resulting solution was stirred at 0 °C for 2.5h. The reaction solution was then poured into 300 ml of water and then 200 ml of ether was added. The layers were separated and the organic phase was washed with water (300 x 5) and dried (Na_2SO_4). After the solvent was evaporated, the residue was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give 35.1g (92%) of the pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.55(d, 3H), 2.40 (s, 3H), 3.91 (q, 1H), 4.18 (m, 4H), 7.12 (m, 2H), 7.24 (m, 2H), 7.37 (d, 1H), 7.66 (d, 1H), 7.70 (m, 4H); MS (ESI) m/z 429 (M+1).

Example 2

Compound 11 (Scheme 2). Compound 11 was prepared as described above for the preparation of compound 10, this time employing naproxen (1) and 1,3-propanediol (3). The resulting compound 11 was purified by crystallization from dichloromethane and hexanes with a 92% yield. ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 3H), 1.78 (m, 2H), 1.87 (br, 1H, D_2O ex), 3.53 (t, 2H), 3.87 (q, 1H), 3.91 (s, 3H), 4.23 (t, 2H), 7.11 (d, 1H), 7.15 (m, 1H), 7.41 (q, 1H), 7.66 (d, 1H), 7.69 (s, 1H), 7.71 (s, 1H); ^{13}C

NMR ($CDCl_3$) δ 18.6, 31.8, 45.7, 55.5, 59.2, 61.9, 77.0, 77.2, 77.5, 105.8, 119.2, 126.1, 126.3, 127.4, 129.1, 129.4, 133.9, 135.7, 157.8, 175.3; and MS (ESI) m/z 289.4 (M+1).

Compound 19 (Scheme 2). Compound 19 was prepared as described above for the preparation of compound 18, this time employing compound 11 and TsCl. Compound 19 was purified by crystallization from ether and hexane with an yield of 95%; ^{1}H NMR ($CDCl_3$) δ 1.54 (d, 3H), 1.91 (m, 2H), 2.42 (s, 3H), 3.79 (q, 1H), 3.92 (s, 3H), 3.99 (t, 2H), 4.10 (t, 2H), 7.11 d, 1H), 7.15 (q, 1H), 7.26 (d, 2H), 7.34 (d, 2H), 7.62(d, 1H), 7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 18.5, 21.8, 28.4, 45.5, 55.5, 60.6, 66.9, 105.8, 119.2, 126.0, 126.3, 127.4, 128.0, 129.1, 129.5, 130.1, 133.1, 133.9, 135.6, 145.0, 157.9, 174.5; MS (ESI) m/z 421.1 (M-1).

Example 3

Compound 12 (Scheme 2). Compound 12 was prepared as described above for the preparation of compound 10, this time employing naproxen (1) and 1,4-butanediol (4). Compound 12 was purified by crystallization from dichloromethane and hexanes with a 90% yield; ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 2H), 1.59 (d, 3H), 1.64 (m, 2H), 1.85 (s, 1H, D_2O, ex), 3.52 (t, 2H), 3.85 (q, 1H), 3.89 (s, 3H), 4.10 (t, 2H), 7.10-7.15 (m, 2H), 7.42 (, d, 1H), 7.66-7.7- (m, 3H); MS (ESI) m/z 325.4 (M+ Na).

Compound 20 (Scheme 2). Compound 20 was prepared as described above for the preparation of compound 18, this time employing compound 12 and TsCl. The compound 20 was purified by crystallization from ether and hexane with an yield of 93%; ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3H), 1.53-1.62 (m, 4H), 2.43 (s, 3H), 3.82 (q, 1H), 3.92 (s, 3H), 3.94 (m, 2H), 4.02 (m, 2H), 7.11-7.15 (m, 2H), 7.30 (d, 2h), 7.38 (d, 1H), 7.64 (d, 1H), 7.70 (d, 2H), 7.75 (d, 2H); MS (ESI) m/z 457.5 (M+1).

Example 4

Compound 13 (Scheme 2). Compound 13 was prepared as described above for the preparation of compound 10, this time employing naproxen (1) and 1,5-

pentanediol (5). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated under high vaccum to give a quantitative yield of the compound 13. The compound was used to make compound 21 without further purification; ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 2H), 1.46 (m, 2H), 1.55 (d, 3H), 1.59 (m, 2H), 3.51 (t, 2H), 3.85 (q, 1H), 3.91 (s, 3H), 4.09 (t, 2H), 7.11-7.15 (m, 2H), 7.40 (q, 1H), 7.66-7.70 (m, 3H); MS (ESI) m/z 317.5 (M+1).

Compound 21 (Scheme 2). Compound 21 was prepared as described above for the preparation of compound 18, this time employing compound 13 and TsCl. Compound 21 was purified by crystallization from ether and hexane with a 95% yield; ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 2H), 1.48-1.58 (m, 4H), 1.59 (d, 3H), 2.43 (s, 3H), 3.84 (q, 1H), 3.89 (t, 2H), 3.91 (s, 3H), 4.01 (t, 2H),7.11-7.15 (m, 2H), 7.32 (q, 2H), 7.39 (q, 1H), 7.65 (d, 1H), 7.70 (m, 2H), 7.75 (d, 2H); MS (ESI) m/z 471.7 (M+1).

Example 5

Compound 14 (Scheme 2). Compound 14 was prepared as described above for the preparation of compound 10, this time employing naproxen (1) and 1,6-hexanediol (6). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound 14 as a solid. The compound was used to make compound 22 without further purification; ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 4H), 1.43 (m 2H), 1.56 (d, 3H), 1.54 (m, 2H), 3.51 (t, 2H), 3.85 (q, 1H), 4.01 (m, 2H), 7.10-7.15 (m 2H), 7.40 (q, 1H), 7.66-7.70 (m, 3H); MS (ESI) m/z 331.7 (M+1).

Compound 22 (Scheme 2). Compound 22 was prepared as described above for the preparation of compound 18, this time employing compound 14 and TsCl. Compound 22 was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give compound 22 as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.12 -1.22 (m, 4H), 1.46-1.52 (m, 4H), 1.57 (d, 3H), 2.43 (s, 3H), 3.84 (q, 1H), 3.92 (s, 3H), 3.93 (m, 2H), 4.03 (m, 2H), 7.11-7.77 (m, 10H); MS (ESI) m/z 485.6 (M+1).

Example 6

Compound 15 (Scheme 2). Compound 15 was prepared as described above for the preparation of compound 10, this time employing naproxen (1) and di(ethylene glycol) (7). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound 15. The compound was used to make compound 23 without further purification; ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3H), 1.93 (br, 1H, D_2O ex), 3.43 (t, 2H), 3.59 (t, 2H), 3.62 (t, 2H), 3.89 (q, 1H), 3.90 (s, 3H), 4.25 (m, 2H), 7.11-7.15 (m, 2H), 7.40-7.42 (m, 1H), 7.70 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 18.7, 45.6, 55.5, 61.8, 64.0, 69.2, 72.4, 76.9, 77.2, 77.5, 105,7, 119.2, 126.2, 126.4, 127.3, 129.0, 133.9, 135.7, 157.9, 174.8; MS(ESI) m/z 319.3 (M+1).

Compound 23 (Scheme 2). Compound 23 was prepared as described above for the preparation of compound 18, this time employing compound 15 and TsCl. Compound 23 was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give the compound as a pale yellow oil with a 93% yield. ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3H), 2.41 (s, 3H), 3.43 (m, 2H), 3.48(m, 2H), 3.84 (q, 1H), 3.86 (s, 3H), 3.94 (t, 2H), 4.10 (m, 2H), 7.10-7.13 (m, 2H), 7.29 (d, 2H), 7.39 (d, 1H), 7.65-7.75 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.6, 21.8, 45.5, 55.5, 63.9, 68.7, 69.27, 69.27, 105.8, 119.2, 126.2, 126.4, 127.4, 128.1, 129.0, 129.4, 129.9, 133.9, 145.0, 157.9, 174.7; MS (ESI) m/z 473.4 (M+1).

Example 7

Compound 16 (Scheme 2). Compound 16 was prepared as described above for the preparation of compound 10, this time employing naproxen (1) and 1,3-pentanediol (8). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound 15 with a 32% yield. The compound was used to make compound 24 without further purification; ^{1}H NMR, ^{13}C NMR and MS are consistent with the structure of compound 16.

Compound 24 (Scheme 2). Compound 24 was prepared as described above for the preparation of compound 18, this time employing compound 16 and TsCl. The compound 24 was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give the compound as a pale yellow oil with a 82% yield. The ^{1}H NMR, ^{13}C NMR and MS are consistent with the structure of compound 24.

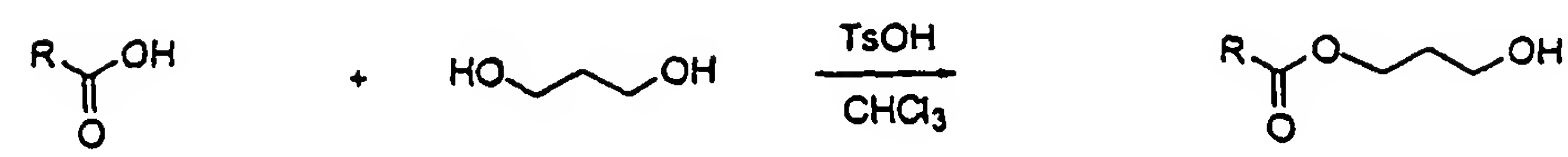
Example 8

Compound 17 (Scheme 2). Compound 17 was prepared as described above for the preparation of compound 10, this time employing naproxen (1) and 1,4-cyclohexanediol (8). After reaction, the reaction solution was washed with water and the reaction solvent was then evaporated to give compound 17. Compound 17 was used to make compound 25 without further purification; ^{1}H NMR ($CDCl_3$) δ 1.30-1.45 (m, 6H), 1.56 (d, 3H), 1.80-1.98 (m, 4H), 3.66 (m, 1H), 3.82 (q, 1H), 3.91 (s, 3H), 4.75 (m, 1H), 7.11 m, 2H), 7.39 (d, 1H), 7.65-7.70 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 18.7, 28.2, 28.5, 32.1, 32.2, 45.9, 55.5, 68.9, 72.0, 76.9, 77.2, 77.5, 105.8, 119.1, 126.0, 126.4, 127.2, 129.1, 129.5, 133.8, 136.1, 157.8, 174.4; MS (ESI) m/z 351.4 (M + Na).

Compound 25 (Scheme 2). Compound 25 was prepared as described above for the preparation of compound 18, this time employing compound 17 and TsCl. Compound 25 was purified by column chromatography on a silica gel column using dichloromethane as an eluent to give the compound as a pale yellow oil with a 93% yield; ^{1}H NMR ($CDCl_3$) δ 1.50-1.84 (m, 11H), 2.43 (s, 3H), 3.80 (q, 1H), 3.92 (s, 3H), 4.51 (m, 1H), 4.78 (m, 1H), 7.10-7.15 (m 2H), 7.26-7.39 (m, 3H), 7.61-7.75 (m, 5H); MS (ESI) m/z 483.5 (M+H).

The syntheses described in Examples 9-14 are outlined in Scheme 3.

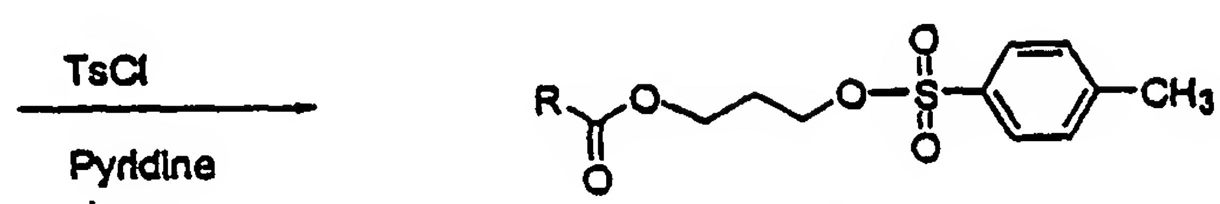
Scheme 3



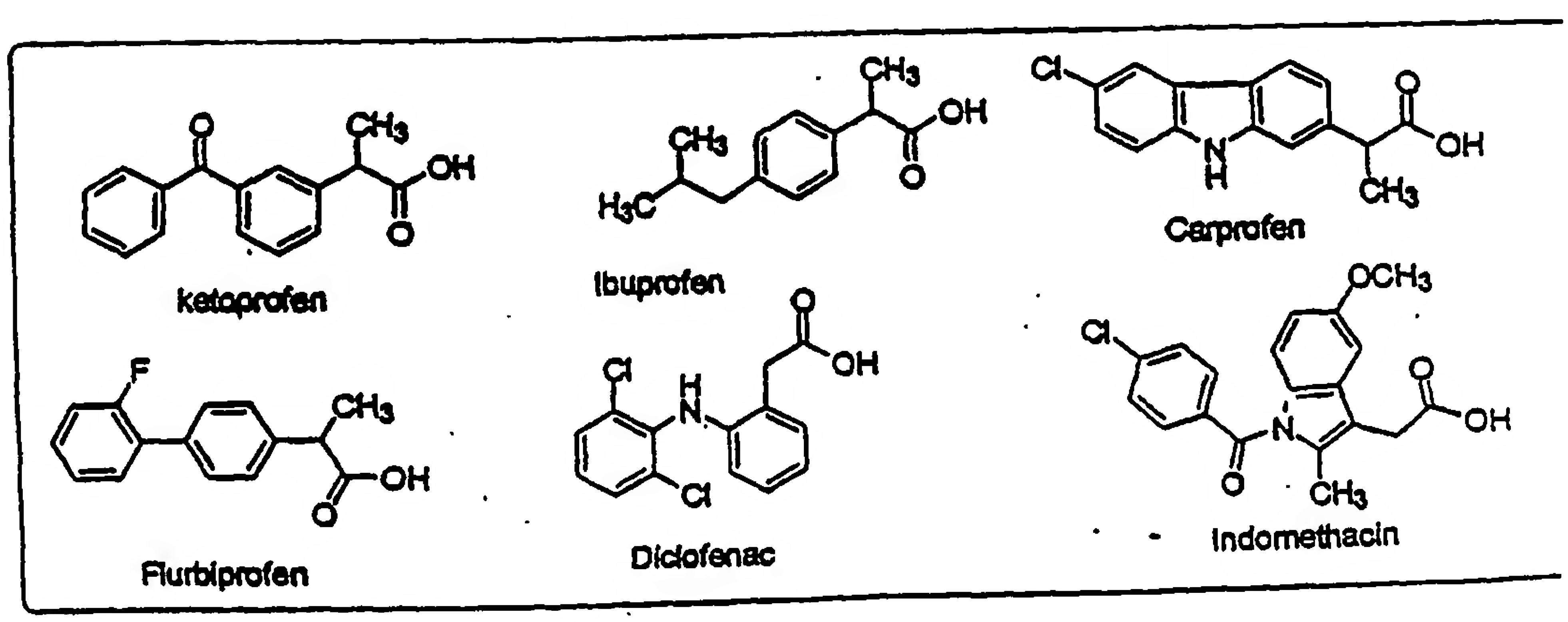
26, R = Ketoprofen
27, R = Flurbiprofen
28, R = Ibuprofen
29, R = Diclofenac
30, R = Carprofen
31, R = Indomethacin

3

32, R = Ketoprofen
33, R = Flurbiprofen
34, R = Ibuprofen
35, R = Diclofenac
36, R = Carprofen
37, R = Indomethacin



38, R = Ketoprofen
39, R = Flurbiprofen
40, R = Ibuprofen
41, R = Diclofenac
42, R = Carprofen
43, R = Indomethacin



Example 9

Compound 32 (Scheme 3). Compound 32 was prepared as described above for the preparation of compound 10, this time employing ketoprofen (26) and 1,3-propanediol (3). Compound 32 was purified by column chromatography on a silica gel column using 200:1 CH_2Cl_2/MeOH as an eluent to give compound 32 with a 50% yield. ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3H), 1.82 (m 3H, 1H, D_2O ex), 3.58 (m, 2H), 3.82(m, 1H), 4.25 (m 2H), 7.44-7.82 (m, 9H); MS (ESI) m/z 313.5 (M+H).

Compound 38 (Scheme 3). Compound 38 was prepared as described above for the preparation of compound 18, this time employing compound 32 and TsCl. Compound 38 was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give the compound 38 as a colorless oil with a 81% yield; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, 3H), 1.94 (m, 2H), 2.43 (s, 3H), 3.72 (q, 1H), 4.01 (t, 2H), 4.12 (m, 2H), 7.31-7.78 (m, 13H); MS (ESI) m/z 467.3 (M+H).

Example 10

Compound 33 (Scheme 3). Compound 33 was prepared as described above for the preparation of compound 10, this time employing flurbiprofen (27) and 1,3-propanediol (3). After reaction, the reaction solution was washed in water and the reaction solvent was then evaporated to give the compound 33 with a quantitative yield. The compound 33 was used to make compound 39 without further purification; ^{1}H NMR ($CDCl_3$) δ 1.54 (d, 3H), 1.79 (t, 1H, D_2O ex), 1.85 (m, 2H), 3.63 (m, 2H), 3.76 (q, 1H), 4.27 (t, 2H), 7.11-7.16(m, 2H), 7.35-7.46 (m, 4H), 7.54 (d, 2H); MS (ESI) m/z 325.4 (M+Na).

Compound 39 (Scheme 3). Compound 39 was prepared as described above for the preparation of compound 18, this time employing compound 33 and TsCl. Compound 39 was purified by crystallization from ether/hexane system with a 79% yield; ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3H), 1.96 (m, 2H), 2.42 (s, 3H), 3.68 (q, 1H), 4.03 (t, 2H), 4.15 (t, 2H), 7.05-7.11 (m, 2H), 7.25-7.54 (m, 8H), 7.76 (d, 2H); ^{13}C NMR

$(CDCl_3)$ δ 18.4, 21.8, 28.4, 45.0, 50.8, 66.9, 115.2, 115.5, 123.68, 123.7, 127.9, 128.0, 129.2, 130.1, 131.0, 133.1, 135.6, 141.75, 141.8, 145.1, 158.9, 160.9, 173.9; MS (ESI) m/z 479.4 (M+Na).

Example 11

Compound 34 (Scheme 3). Compound 34 was prepared as described above for the preparation of compound 10, this time employing ibuprofen (28) and 1,3-propanediol (3). After reaction, the reaction solution was washed in water and the reaction solvent was then evaporated to give compound 34 with a quantitative yield. The compound 34 was used to make compound 40 without further purification; ^1H NMR $(CDCl_3)$ δ 0.89 (d, 6H), 1.49 (d, 3H), 1.79 (t, 2H), 1.78-1.85 (m, 1H), 1.95 (t, 1H, D_2O ex), 2.45 (d, 2H), 3.53 (m, 2H), 3.71 (q, 1H), 4.22 (m, 2H), 7.09 (d, 2H), 7.26 (d, 2H).

Compound 40 (Scheme 3). Compound 40 was prepared as described above for the preparation of compound 18, this time employing compound 34 and TsCl. Compound 40 was purified by crystallization from ether/hexane system to give a white solid with a 96% yield; ^1H NMR $(CDCl_3)$ δ 0.89 (d, 6H), 1.44 (d, 3H), 1.81-1.92 (m, 3H), 2.44 (s, 3H), 3.61 (q, 1H), 3.99 (t, 2H), 4.09 (t, 2H), 7.08 (d, 2H), 7.14 (d, 2H), 7.34 (d, 2H), 7.78 (d, 2H); ^{13}C NMR $(CDCl_3)$ δ 18.46, 21.80, 22.54, 28.39, 30.32, 45.16, 60.39, 66.92, 127.23, 128.04, 129.50, 130.03, 133.12, 137.68, 140.76, 145.00, 174.54; MS (ESI) m/z 441.5 (M + Na).

Example 12

Compound 35 (Scheme 3). Compound 35 was prepared as described above for the preparation of compound 10, this time employing diclofenac (29) and 1,3-propanediol (3). After reaction, compound 35 was purified by column chromatography on a silica gel column using 200:1 CH_2Cl_2/MeOH as an eluent to give the compound 35 as a white solid with a 56% yield. ^1H NMR $(CDCl_3)$ δ 1.89 (m, 3H, 1H D_2O ex), 3.66 (t, 2H), 3.83 (s, 3H), 4.31 (t, 2H), 6.55 (d, 1H), 6.87 (br, 1H),

6.94-7.00 (m, 2H), 7.11-7.14 (m, 1H), 7.22-7.26 (m, 1H), 7.34 (d, 2H); MS (ESI) m/z 376.3 (M+Na).

Compound 41 (Scheme 3). Compound 41 was prepared as described above for the preparation of compound 18, this time employing compound 35 and TsCl. Compound 41 was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give the compound 41 as a pale yellow oil and the yield was 89% ; ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 2H), 2.43 (s, 3H), 3.73 (s, 2H), 4.09 (t, 2H), 4.17 (t, 2H), 6.53 (d, 1H), 6.99 (s, 1H), 6.93-7.00 (m, 2H), 7.12 (t, 1H), 7.18 (d, 1H), 7.23 (d, 1H), 7.31-7.35 (m, 3H), 7.78 (d, 2H); MS (ESI) m/z 508.3 (M).

Example 13

Compound 36 (Scheme 3). Compound 36 was prepared as described above for the preparation of compound 10, this time employing carprofen (30) and 1,3-propanediol (3). After reaction, compound 36 was purified by column chromatography on a silica gel column using 200:1 CH_2Cl_2/MeOH as an eluent to give the compound 36 as a colorless oil with a 54% yield. ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 3H), 1.74 (br, 1H, D_2O ex), 1.80 (m, 2H), 3.53-3.56 (m, 2H), 3.88 (q, 1H), 4.22-4.28 (m, 2H), 7.17 (d, 1H), 7.29-7.35 (m, 3H), 7.94-7.98 (m, 2H), 8.14 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 18.99, 31.84, 46.17, 59.42, 62.10, 109.70, 111.79, 119.79, 120.21, 120.87, 121.92, 124.49, 125.22, 126.09, 138.24, 139.37, 140.55, 175.39; MS (ESI) m/z 332.2 (M+H).

Compound 42 (Scheme 3). Compound 42 was prepared as described above for the preparation of compound 18, this time employing compound 36 and TsCl. Compound 42 was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give the compound 42 as a sticky oil and the yield was 90% ; ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3H), 1.91 (m, 2H), 2.39 (s, 3H), 3.83 (q, 1H), 3.97 (t, 2H), 4.09-4.18 (m, 2H), 7.10 (d, 1H), 7.21(d, 2H), 7.32 (s, 2H), 7.38 (s, 1H)7.65 (d, 2H), 7.91 (d, 1H), 7.98 (s, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.83, 21.77, 28.32,

46.08, 60.59, 57.04, 109.97, 111.97; 119.58, 120.06, 120.69, 121.77, 124.38, 125.00, 125.99, 127.95, 129.22, 130.06, 132.90, 138.38, 139.19, 140.69, 145.15, 174.59; MS (ESI) m/z 486.3 (M +H).

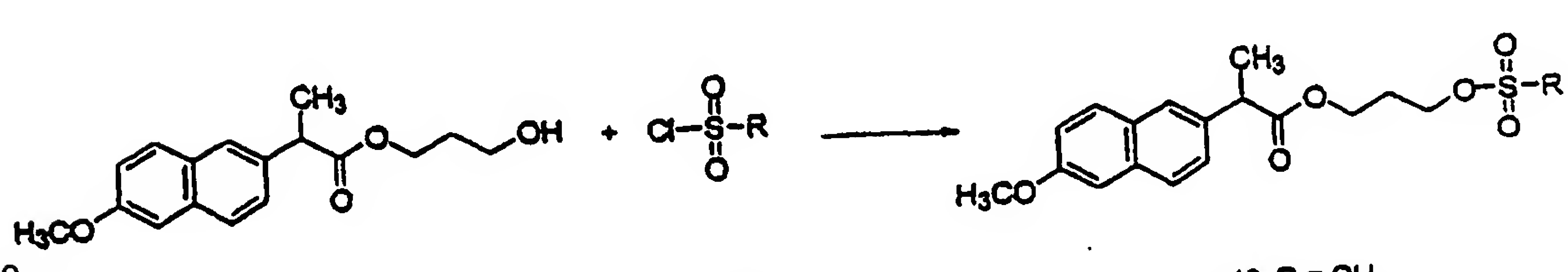
Example 14

Compound 37 (Scheme 3). Compound 37 was prepared as described above for the preparation of compound 10, this time employing indomethacin (31) and 1,3-propanediol (3). After reaction, compound 37 was purified by column chromatography on a silica gel column using 200:1; 100:1 CH_2Cl_2/MeOH as an eluents to give the compound 37 as a pale yellow oil with a 49% yield. ^{1}H NMR, ^{13}C NMR and MS are consistent with the structure of compound 37.

Compound 43 (Scheme 3). Compound 43 was prepared as described above for the preparation of compound 18, this time employing compound 37 and TsCl. The compound 43 was purified by column chromatography on a silica gel column using hexane/ethyl acetate (3:1) as an eluent to give the compound 43 as a pale yellow oil and the yield was 71% ; ^{1}H NMR ($CDCl_3$) δ 1.97 (m, 2H), 2.36 (s, 3H), 2.44 (s, 3H), 3.63 (s, 2H), 3.83 (s, 3H), 4.05 (t, 2H), 4.15 (t, 2H), 6.66-6.68 (m, 1H), 6.87 (d, 1H), 6.93 (d, 1H), 7.33 (d, 2H), 7.47 (d, 2H), 7.67 (d, 2H), 7.75 (d, 2H); MS (ESI) m/z 592.0 (M + Na).

The syntheses described in Examples 15 and 16 are outlined in Scheme 4.

Scheme 4



11

44, R = CH_3
45, R = CF_3

46, R = CH_3
47, R = CF_3

Example 15

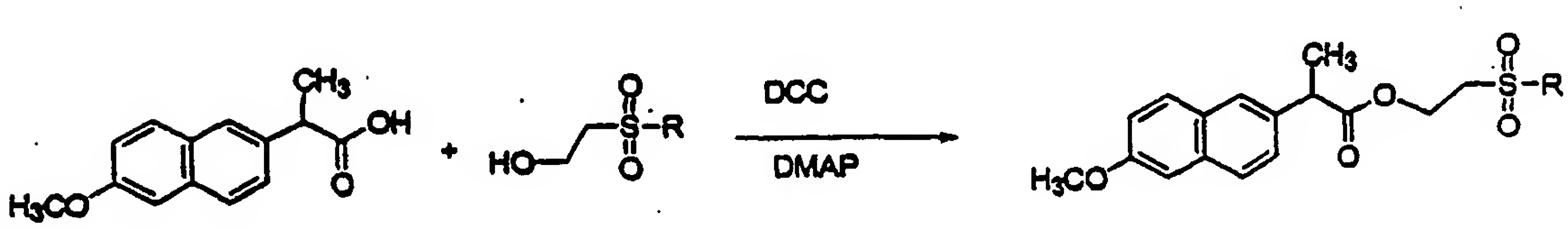
Compound 46 (Scheme 4). Compound 46 was prepared as described above for the preparation of compound 18, this time employing compound 11 and 44. The compound 46 was purified by crystallization from ether/hexane system to give the compound 46 as a white solid . The yield was 95%; ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3H), 2.00 (m, 2H), 2.73 (s, 3H), 3.87 (q, 1H), 3.90 (s, 3H), 4.10 (t, 2H), 4.18 (t, 2H), 7.10-7.15 (m, 2H), 7.39 (d, 1H), 7.66-7.71 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 18.46, 28.55, 37.03, 45.56, 55.47, 55.50, 60.38, 66.36, 105.75, 119.32, 126.09, 126.27, 127.44, 129.06, 129.41, 133.89, 135.68, 157.91, 174.59; MS (ESI) m/z 388.5 (M + Na).

Example 16

Compound 47 (Scheme 4). Compound 47 is prepared as described above for the preparation of compound 18, this time employing compound 11 and compound 45. The compound is purified by crystallization and the yield was 70-90%. The ^{1}H NMR, ^{13}C NMR and MS are consistent with the structure of compound 47.

The syntheses described in Examples 17 and 18 are outlined in Scheme 5.

Scheme 5



1

48, R = CH_3
49, R = m-$C_6H_4NO_2$

50, R = CH_3
51, R = m-$C_6H_4NO_2$

Example 17

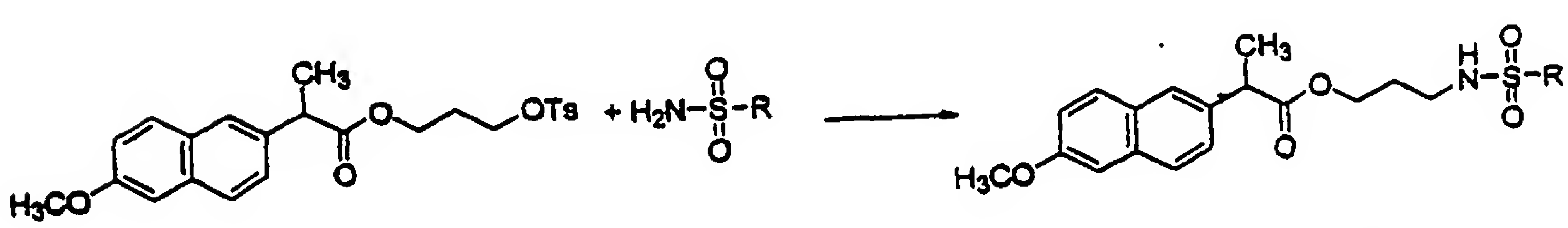
Compound 50 (Scheme 5). To a solution of naproxen (1) (1.15g, 5 mmol), compound 48 (0.62g, 5 mmol) and dimethylamino pyridine (DMAP) (0.12g, 1 mmol) was added dicyclohexyldicarbodiimide (DCC) (1.03g, 5 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1.5 h. After reaction, the solid was filtered off and the solvent was evaporated. The residue was washed with ether to give 1.4g (83%) of compound 50 as a white solid; ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 3H), 2.38 (s, 3H), 3.17 (m, 2H), 3.87 (q, 1H), 3.92 (s, 3H), 4.43 (m, 1H), 4.59 (m, 1H), 7.10 (d, 1H), 7.15 (m, 1H), 7.33 (m, 1H), 7.67 (d, 1H), 7.70 (m, 2H); MS (ES) m/e 358.2 (M+Na).

Example 18

Compound 51 (Scheme 5). Compound 51 was prepared as described above for the preparation of compound 50, this time employing compound 1 (1.15g, 5mmol) and 49 (1.16g, 5 mmol). The compound was purified by column chromatography on a silica gel column using 1:1 hexanes/ethyl acetate as eluent to give 0.91g of compound 51 as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.45 (d, 3H), 3.48 (m, 2H), 3.59 (q, 1H), 3.92 (s, 3H), 4.47 (m, 2H), 7.10 (d, 1H), 7.18 (m, 2H), 7.45 (s, 1H), 7.49 (t, 1H), 7.65 (t, 2H), 8.06 (q, 1H), 8.28 (q, 1H), 8.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.8, 45.2, 55.4, 55.5, 57.9, 105,8, 123.6, 125.9, 127.5, 128.4, 129.0, 129.3, 130.8, 133.7, 133.9, 134.9, 141.5, 148.4, 158.0, 174.0.

The syntheses described in Examples 19-21 are outlined in Scheme 6.

Scheme 6



19

52, R = CH_3
53, R = p-C_6H_4Me
54, R = o- $C_6H_4NO_2$

55, R = CH_3
56, R = p-C_6H_4Me
57, R = o- $C_6H_4NO_2$

Example 19

Compound 55 (Scheme 6). A mixture of compound 19 (2.2g, 5 mmol), compound 52 (0.57g, 6mmol) and K_2CO_3 (3.45g, 25 mmol) in 50 ml of dimethyl formamide (DMF) was stirred for a week. The reaction solution was poured into 100 ml of water and extracted with CH_2Cl_2. The organic phase was washed with water (50 x 5) and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography on a silica gel column using 3:1 hexane/ ethyacetate as an eluent to give 0.3g (16%) of compound 55 as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.60 (d, 3H), 2.38 (s, 3H), 3.17 (m, 2H), 3.87 (q, 1H), 3.92 (s, 3H), 4.45 (m, 1H), 4.59 (m, 1H), 7.10 (s, 1H), 7.14-7.16 (q, 1H), 7.32-7.35 (q, 1H), 7.62 (s, 1H), 7.67-7.71 (m, 2H); MS (ESI) m/z 358.2 (M + Na).

Example 20

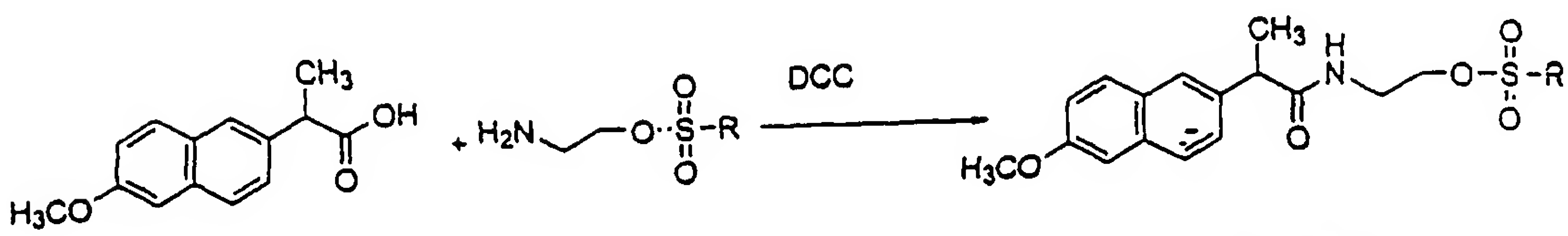
Compound 56 (Scheme 6). Compound 56 was prepared as described above for the preparation of compound 55, this time employing compound 19 and compound 53. The compound was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give compound 56 as a pale yellow oil (33%). ^{1}H NMR ($CDCl_3$) δ 1.54 (d, 3H), 1.72 (m, 2H), 2.83 (m, 2H), 3.80 (q, 1H), 3.92 (s, 3H), 4.10 (t, 2H)7.07-8,10 (m, 10H); MS (ESI) m/z 442.3 (M + H).

Example 21

Compound 57 (Scheme 6). Compound 57 was prepared as described above for the preparation of compound 55, this time employing compound 19 and compound 54. The compound was purified by column chromatography on a silica gel column using CH_2Cl_2 as an eluent to give compound 57 as a pale yellow oil (11%). ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3H), 1.80 (m, 2H), 3.03 (m 2H),3.86 (m, 1H), 4.13 (m, 2H), 7.07-7.93 (m, 10H); MS (ESI) m/z 473.4 (M + H).

The syntheses described in Examples 22 and 23 are outlined in Scheme 7.

Scheme 7



1

58, R = CH_3
59, R = p-C_6H_4Me

60, R = CH_3
61, R = p-C_6H_4Me

Example 22

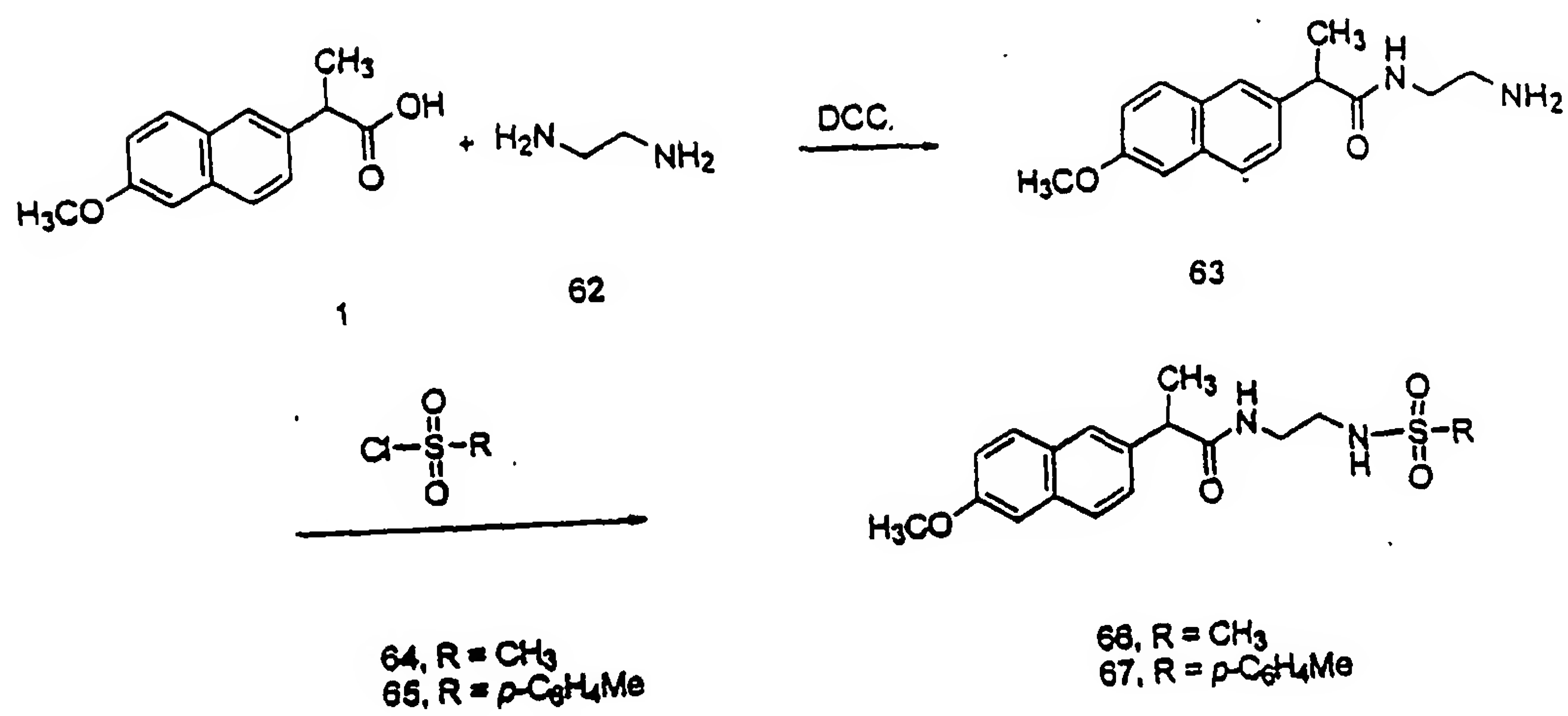
Compound 60 (Scheme 7). Compound 60 is prepared as described above for the preparation of compound 50, this time employing naproxen 1 and compound 58. After reaction the compound is purified by column chromatography on a silica gel column to give the compound 60 in a yield from 75 -95%.

Example 23

Compound 61 (Scheme 7). Compound 61 is prepared as described above for the preparation of compound 50, this time employing naproxen (1)and compound 59. After reaction, the compound is purified by column chromatography on a silica gel column to give compound 61 in a yield from 75 -95%.

The syntheses described in Examples 24 and 25 are outlined in Scheme 8.

Scheme 8



Example 24

Compound 63 (Scheme 8). Compound 63 is prepared as described above for the preparation of compound 50, this time employing naproxen (1) and compound 62. After reaction, the compound is purified by column chromatography on a silica gel column to give compound 63 in a yield of 75 -95%.

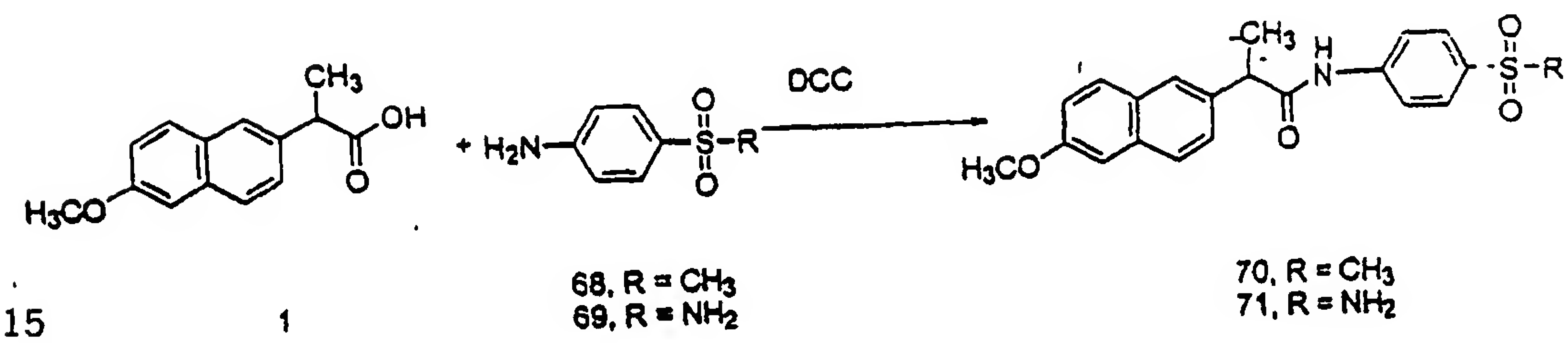
Compound 66 (Scheme 8). Compound 66 is prepared as described above for the preparation of compound 18, this time employing compound 63 and compound 64.

Example 25

Compound 67 (Scheme 8). Compound 67 is prepared as described above for the preparation of compound 18, this time employing compound 63 and compound 65.

The syntheses described in Examples 26 and 27 are outlined in Scheme 9.

Scheme 9



Example 26

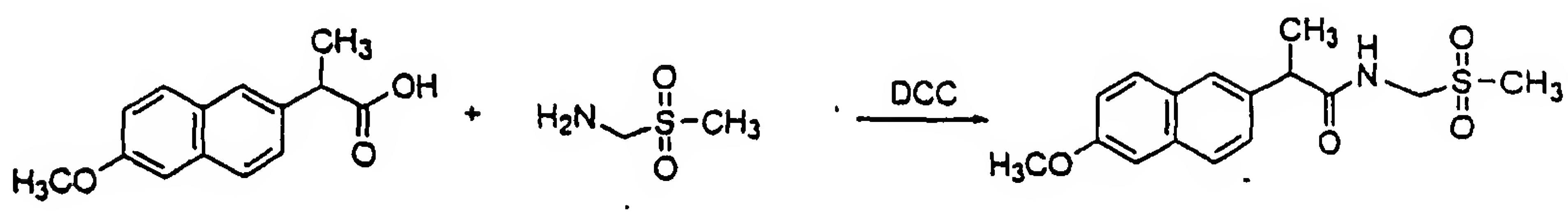
Compound 70 (Scheme 9). Compound 70 is prepared as described above for the preparation of compound 60, this time employing compound 1 and compound 68.

Example 27

Compound 71 (Scheme 9). Compound 71 is prepared as described above for the preparation of compound 60, this time employing compound 1 and compound 69.

The synthesis described in Example 28 is outlined in Scheme 10.

Scheme 10



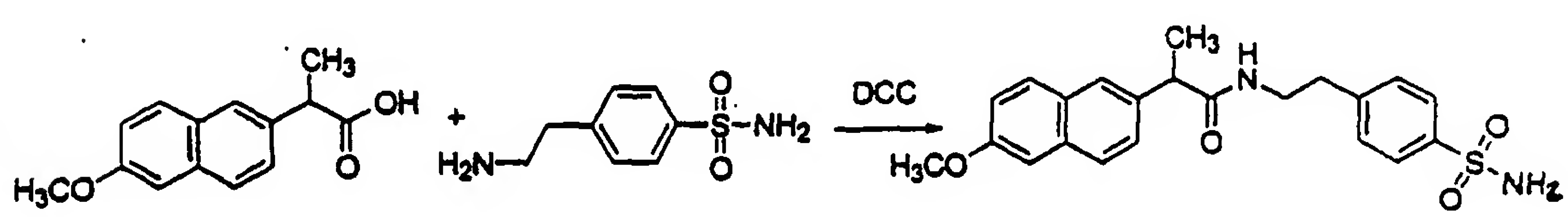
1 72 73

Example 28

Compound 73 (Scheme 10). Compound 73 is prepared as described above for the preparation of compound 60, this time employing compound 1 and compound 72.

The synthesis described in Example 29 is outlined in Scheme 11.

Scheme 11



1 74 75

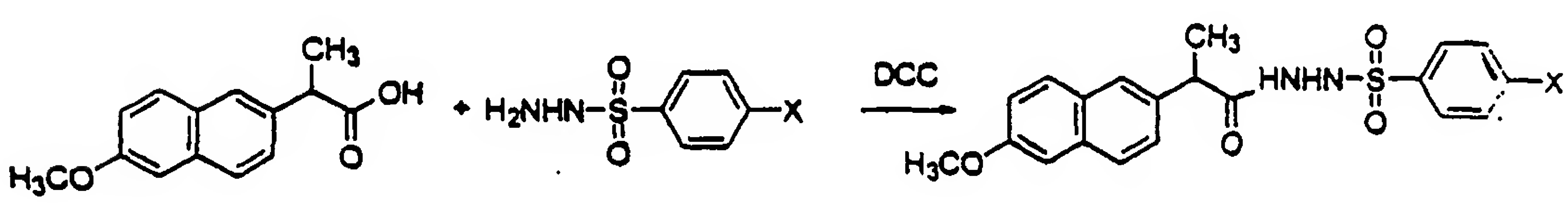
Example 29

Compound 75 (Scheme 11). To a solution of naproxen **1** (1.15g, 5.0 mmol) and 1,3-dicyclohexylcarbodiimide (DCC) (1.03g, 5mmol) in 180 ml of anhydrous tedrahydrofuran (THF) was added 4-(2-aminoethyl)benzenesulfonamide **74** (1.1g, 5.5 mmol) at rt. The resulting mixture was stirred overnight. The resulted solid was filtered off and the solvent was evaporated. The residue was partially dissolved in ethyl acetate and filtered to remove more solid. The filtrate was evaporated and the

residue was purified by flash chromatography on a silica gel column using CH_2Cl_2 and 100:1 CH_2Cl_2-MeOH as eluents to give 0.1g (5%) of the compound **75** as a white solid; ^{1}H NMR (DMSO-d_6) δ 1.38 (d, 3H), 2.73 (m, 3H, 1H, ex D_2O), 3.68 (q, 1H), 3.86 (s, 3H), 7.13-8.08 (m, 12H, 2H, ex D_2O); MS (ESI) *m/z* 413.1 (M + H)$^+$ ($C_{22}H_{25}N_2O_4S$ requires 413.5).

The syntheses described in Examples 30 and 31 are outlined in Scheme 12.

Scheme 12



1

76 X = H
77 X = OCH$_3$

78 X = H
79 X = OCH$_3$

Example 30

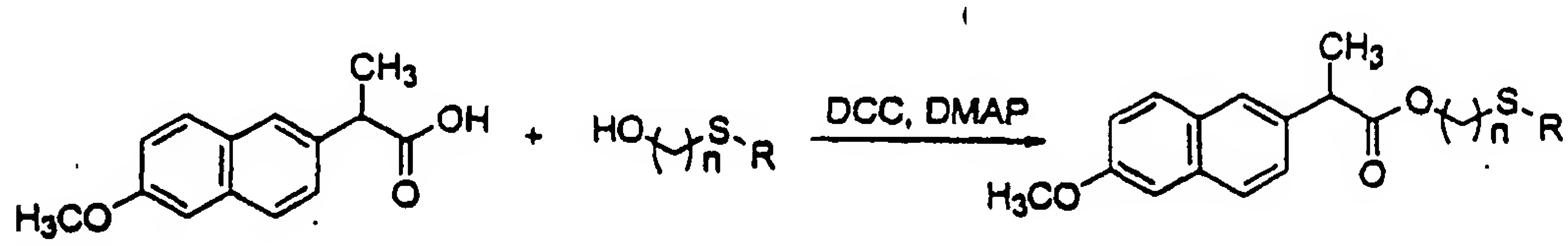
Compound 78 (Scheme 12). To a solution of naproxen **1** (1.15g, 5 mmol) and benzenesulfonyl hydrazide **76** (0.86g, 5 mmol) in 50 ml of CH_2Cl_2 was added DCC (1.03g, 5 mmol) at rt. The resulting solution was stirred at rt for 26 h. The resulted solid was filtered off and the filtrate was washed with 5% Na_2CO_3 solution, 0.5N HCl solution and water. The organic phase was dried with anhydrous sodium sulfate (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on a silica gel column using 5:1 and 2:1 hexanes-EtOAc as eluents to give 1.44g (75%) of the compound **78** as a white solid; ^{1}H NMR ($CDCl_3$) δ 1.37 (d, 3H), 3.54 (q, 1H), 3.94 (s, 3H), 7.12-7.77 (m, 13H, 2H, ex D_2O); MS (ESI) *m/z* 385.0 (M + H)$^+$ ($C_{20}H_{21}N_2O_4S$ requires 385.1).

Example 31

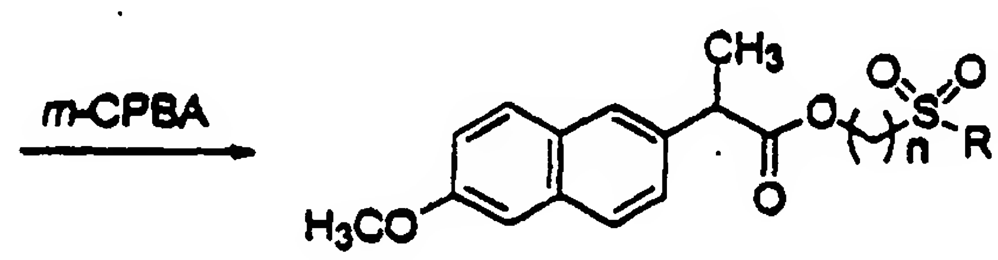
Compound 79 (Scheme 12). Compound **79** was prepared by the similar procedure as described above for compound **78** from 4-methoxybenzenesulfonyl hydrazide **77** (1.01g, 5 mmol), naproxen **1** (1.15g, 5 mmol) and DCC (1.03g, 5 mmol). The compound was purified by flash chromatography on a silica gel column using 200:1 CH_2Cl_2-MeOH as an eluent to give 0.69g (33%) of the compound **79** as a white solid; ^{1}H NMR ($CDCl_3$) δ 1.38 (d, 3H), 3.57 (q, 1H), 3.68 (s, 3H), 3.92 (s, 3H), 6.60-8.13 (12H, 2H ex D_2O); MS (ESI) *m/z* 415.7 $(M + H)^+$ ($C_{21}H_{23}N_2O_5S$ requires 415.2).

The syntheses described in Examples 32-35 are outlined in Scheme 13.

Scheme 13



1 **80 n = 2, R = CH_3** **84 n = 2, R = CH_3**
81 n = 3, R = CH_3 **85 n = 3, R = CH_3**
82 n = 4, R = CH_3 **86 n = 4, R = CH_3**
83 n = 2, R = C_6H_5 **87 n = 2, R = C_6H_5**



50 n = 2, R = CH_3
88 n = 3, R = CH_3
89 n = 4, R = CH_3
90 n = 2, R = C_6H_5